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DISEASES DUE TO MEDICAL TREATMENT*

BY

C. BRUCE PERRY

The concept that illness may result from medical treatment is not so modern as might at first be thought. Probably cynics have long suspected that this might be so, and in the seventeenth century we find Argan in Molière's play *Le malade imaginaire* saying to Beralde—the serious brother—"Tell me what do you do when you are ill" to which the reply is "Nothing, nothing at all. If you are ill just keep quiet and don't fuss. Let nature take her course, leave her alone to do what is necessary to repair your trouble. It is our own uneasiness and our impatience which is our undoing. Most people die of the remedy not of the disease". However, whatever may have been the state of affairs in seventeenth-century France there has been a great increase in complications of drug therapy during the last thirty years which has coincided with the introduction of new anti-bacterial, anti-convulsant, anti-hypertensive, anti-arthritic, anti-thyroid agents, not to mention tranquillizers and cortico-steroids (Brown, 1959). In fact Moser (1959) has recently published a book on this subject entitled *Diseases of Medical Progress*.

Medical treatment and the general management of the patient may produce illness or disease in various ways and the illness produced may be either organic or psychological. The ill effects may be the result of drugs, physical agents or the doings or sayings of the doctor himself. As this discussion is concerned with illness resulting from medical treatment there is no place for discussing the many and varied unfortunate happenings that may occur to the patient after various surgical procedures except to remind you that they are not unknown. Neither is it proposed to discuss poisoning caused by an accidental or careless overdosage of a drug or the inadvertent administration of the wrong drug. Apart from such "accidents" illness may follow the administration of drugs or therapeutic procedures in various ways.

Toxicity may occur with prolonged administration as for instance with digitalis. Another group of illnesses due to drugs results when the drug is given without sufficient safeguards, in excessive dosage or for too long a time. Crystallisation of acetylated derivatives of sulphonamides in the renal tubules may occur in anyone even if receiving the correct dosage of the drug unless adequate steps are taken to see that the patient does not become dehydrated. The hypo-prothrombinaemia and the resulting haemorrhagic state which may complicate massive salicylate therapy is clearly related to an excessive concentration of the drug in the blood and, of course, forms a considerable hazard to the intravenous administration of salicylates in acute rheumatism, which had such a vogue in certain countries some years ago. More recently fatal cases of nephritis have been described in patients taking phenacetin over a long period of time. One such patient who finally died consumed 3·5 kg. of Phenacetin in five and a half years (Moolten and Smith, 1960). It has been suggested that the renal lesion is due to the long continued methaemoglobinaemia produced by the drug. Such conditions as the pulmonary fibrosis following the prolonged use of hexamethonium for hypertension and the syndrome indistinguishable form systemic lupus erythematosus that occurs so frequently after the continued use of hydrallazines may be similar but are so far unexplained.

The patient may show an abnormal response to a drug which is qualitative in nature —an idiosyncrasy—as when barbiturates give rise to excitement. This is clearly

*A paper read at the B.M.A. Annual Meeting, Torquay, 21st June 1960.

due to an abnormality in the patient, the nature of which is far from clear and which may be related to the differing effect of certain drugs in different species.

All patients vary to some extent in their reaction to drugs and in some this intolerance may be so marked that what would be a small dose for a normal individual produces symptoms of poisoning in the susceptible. It is well known for instance that an occasional patient will develop deafness and tinnitus after a therapeutic dose of quinine. In fact it may be very difficult to decide whether the patient's reaction to the drug is within the range of normal variation or is in fact a manifestation of a real intolerance. Perhaps there is no dividing line. Thus it would appear that the macrocytic anaemia which sometimes complicates the use of anti-convulsants such as phenytoin and even phenobarbitone merely represents one extreme of a constant effect of these drugs. Careful studies of large groups of patients receiving them have shown that while relatively few develop anaemia, in the majority a macrocytosis will be found if this is looked for carefully (Hawkins and Meynall, 1958). However with some drugs severe and devastating results occur in the occasional patient which are not seen in others even after larger doses and long continued administration. For instance some patients can take cinchophen and dinitrophenol with apparent impunity while in others either drug may be rapidly fatal from acute necrosis of the liver. Although in many cases it may be difficult to exclude the possibility of the ill effects resulting from some form of "sensitisation" it is probable that in fact we are dealing with an extreme degree of intolerance. It may be that these unfortunate effects in certain people are due to the fact that patients exhibiting such intolerance have a genetic abnormality resulting in a deficiency of an enzyme which protects non-susceptible individuals. It has been claimed that patients who develop haemolytic anaemia after the administration of primaquine are deficient in a specific enzyme—glucose-6-phosphate dehydrogenase—which normally maintains glutathione in the red cells in a reduced form (Carson *et al*, 1956). This defect has more recently been demonstrated in patients developing haemolytic anaemia after various other drugs including sulphonamides (Szeinberg *et al*, 1957; Beutler, 1959).

However in many cases of the diseases due to drugs there is reason to believe that the underlying mechanism is some form of sensitization (Carr, 1951). It is particularly this type of reaction that is common with the newer synthetic drugs. It is clear that the drug itself, not being a protein, cannot act as an antigen but the drug or one of its degradation products may act as a "hapten" and unite with one of the patient's own proteins which will then be "foreign" and become antigenic. It appears that drugs containing a pyrimidine or "benzamine" grouping are particularly likely to act as a hapten in this way (Samter and Berryman, 1958). There is good evidence for this theory of sensitization in such reactions as are characterized by urticarial rashes, dermatitis, angioneurotic oedema or asthma. Very often there is a history of a previous administration of the drug.

While the basis of this type of sensitivity reaction which follows the second administration of the drug after an interval may be fairly simple to understand, it is more difficult to see exactly what happens in the more common phenomenon where the patient becomes sensitized while still receiving, or still in contact with, the sensitizing agent. Perhaps the best example of this is the long recognized serum sickness, characterized, usually, by urticarial rash, fever, arthritis and adenopathy, occurring about ten days after an injection of foreign serum, and while the causal foreign serum must still be present in the blood stream to excite the reaction. Similar to this are the "drug rashes" and "fevers" seen with so many of our modern drugs, particularly the sulphonamides, and which usually occur five to ten days after the drug was first given even if it has subsequently been stopped. However it is difficult to explain the occasional occurrence of such phenomena after the first dose of a drug in a patient who has never received it previously. It has been suggested that when this happens with penicillin the patient may have become sensitized by exposure to the mould

from which penicillin is derived. But it is difficult to explain the fever and massive urticaria which occur not very rarely within a few hours of the first dose of a new drug such as dindevan which the patient can hardly have met previously. Rarely such hypersensitivity reactions may be fatal as when a patient is given a second injection of antitoxin prepared from horse serum some months or years after the first. This serves to remind us that such unhappy events might often be prevented with a little care and forethought. For instance when analysing thirty fatal reactions to penicillin Rosenthal (1958) found that in fourteen no enquiry had been made as to whether the patient had ever received penicillin before, and in ten the patients had in fact had lesser reactions to penicillin on previous occasions.

While discussing this problem of sensitization to drugs it is perhaps worth while stressing the fact that sensitization is far more likely to occur when the drug is given by some routes than by others. Thus penicillin and sulphonamide sensitization occur relatively frequently if the drug is applied to the skin, and fortunately comparatively infrequently when administered by mouth or by injection. For this reason it is always preferable to treat skin sepsis by systemic rather than local administration of these drugs. Similar sensitization may follow the surface application of local anaesthetics such as benzocaine, yet the subcutaneous administration of the same substance seems relatively immune from this risk.

However, many of the diseases which follow administration of drugs and which we believe to be due to sensitization are less easy to understand and are far more complex. There seems to be little doubt that polyarteritis nodosa has followed second administration, after an interval, of both sulphonamides and thiouracils. While we can understand how the drug assumes antigenic properties by becoming conjugated with one of the patient's own proteins it is difficult to see why the arteries in this particular case are singled out. Ackroyd's work (1953) on thrombocytopenic pupura following sedormid has shown clearly that sedormid causes platelet lysis in the blood of sensitized patients and it would appear that sedormid unites with platelets to constitute an antigen which stimulates the formation of antibody which in the presence of complement lyses the antigen (i.e. the "sedormized" platelets). It is probable that this combination always happens whenever sedormid comes into contact with platelets. The fact that only a few of the patients who take the drug develop purpura may be due to the compound being a substance of low antigenicity which stimulates antibody formation only in patients whose immunity reactions are readily stimulated by so weak an antigen. The work of Bolton (1956) demonstrates that a similar mechanism operates in thrombocytopenia due to quinine, and there is good reason to suppose that the thrombocytopenia that follows the administration of some other drugs has the same basis. The experiments of Steinkamp, Moore and Doubek (1955) show that the antibody in a patient with thrombocytopenic purpura due to quinine can be transferred passively in the patient's serum so that a recipient who is taking quinine develops thronbocytopenia and purpura. The nature of the jaundice which may follow the use of chlorpromazine and similar "tranquillizers" and which was originally thought to be due to a fairly benign cholangiolytic process but which recent work shows is in fact associated with necrosis of liver cells (Zelmann, 1959) is not altogether clear. But the following case history strongly suggests that it too is a sensitization phenomenon. A patient with recurrent attacks of endogenous depression was referred some two years ago for unexplained recurrent jaundice. She first developed jaundice after receiving chlorpromazine for some time. The drug was stopped and the jaundice cleared but the association between the two was not recognized. Some six months later there was a return of depression and chlorpromazine was again prescribed but this time jaundice developed after the second dose of the drug.

Another group of illnesses due to treatment is that comprising diseases which result from side effects of drugs. We have long recognized the dry mucous membranes that follow the use of atropine in full doses, and the somnolence caused by antihist-

amines is so well recognized that they are now sometimes used as mild hypnotics. Antibiotics by destroying useful commensals in the alimentary canal in addition to the pathogenic organisms giving rise to the disease for which they are prescribed may give rise to the troublesome ano-rectal syndrome, may allow monilia to proliferate or, even more serious, allow resistant staphylococci to flourish and so produce a fatal enteritis. The emergence of drug resistant organisms and the occurrence of illness due to infection with the organisms is clearly another example of undesirable side effects of the use of invaluable antibiotics. Similar undesirable "side effects" are probably responsible for the severe depression that may follow the use of rauwolfia and its derivatives. Chlorpromazine and its allies may in the same way give rise to Parkinsonism which may so closely mimic that due to encephalitis lethargica as to be associated with oculo-gyral crises. In the same way the therapeutic use of steroids may produce a clinical picture closely resembling Cushing's syndrome, perforation of peptic ulcer, osteoporosis with collapse of vertebrae and the masking of intercurrent infection. Another troublesome complication of steroid therapy is the exacerbation of the treated disease that so commonly follows withdrawal of the drug. But this phenomenon is not peculiar to the steriods for it may also occur, but usually to a lesser degree, when salicylates are stopped in patients with acute rheumatism. A much more serious effect of prolonged steroid therapy is the severe depression of suprarenal function which makes the patient extremely vulnerable to any stress in the shape of infection, anaesthesia or surgical operation (Allanby, 1957; Bayliss, 1958; Dundee, 1958). Another example of the results of successful "treatment" giving rise to new illness is the haemorrhagic state that may occur with anticoagulant therapy, which may cause for example haemorrhagic pericarditis in patients with mycordial infarction, or bleeding from an unsuspected peptic ulcer. Similarly the successful reduction of blood pressure by hypotensive drugs may precipitate the onset of renal failure (Carter and Payne, 1956) or myocardial ischaemia (Judson *et al*, 1956) in patients whose renal or coronary circulation has only been adequately maintained hitherto by means of the hypertension.

The use of X-rays and other radio-active agents may also cause disease. Whether or not X-ray therapy affects the course of ankylosing spondylitis there seems to be little doubt that patients so treated are far more likely to develop leukaemia than the normal population. Twenty years ago there was a vogue for the irradiation of babies with supposedly enlarged thymus, especially in the United States, and this has been followed by a slight but definite increase in the incidence of carcinomata and adenomata of the thyroid and of leukaemia in these patients. (Simpson *et al.*, 1955). Similar to this is the malignant disease which so frequently followed the use of thorotrast as a contrast medium in radiology. Fortunately this hazard is now so well known that its use for this purpose has been discarded.

A further group of diseases due to treatment arises from the excessive use of substances which in moderation may be beneficial and which have previously been considered harmless, on the view that one cannot have too much of a good thing. A clear example of this is the tragedy of retrolental fibroplasia with resulting blindness which we now realise was due to exposing premature babies to too high a concentration of oxygen. The assumption that vitamins are always beneficial, no matter in what dose they may be taken, has probably been responsible for more than one "new" disease. There is good reason to believe that the severe jaundice giving rise to kernicterus in premature babies is largely due to the over enthusiastic use of "synkavit" given in an attempt to avoid the possible risk of haemorrhagic disease of the newborn. So too nephrocalcinosis, another new disease of infancy, may well be the result of poisoning with vitamin D which, as well as being enthusiastically prescribed by doctors was at one time added to all sorts of infant foods by the manufacturers. One other example of disease resulting from the administration of apparently harmless drugs is pink disease which was once so common in paediatric practice and the nature and

cause of which was so baffling. The recognition that this might be the result of chronic poisoning with mercury often given in the shape of proprietary "teething powders" led to the mercury being omitted from such powders and the sudden disappearance of the disease.

So much for a few of the diseases that may follow the administration of drugs; but before concluding I would like to refer to two other ways in which treatment may give rise to disease. Firstly it is important to remember that infection may be spread by the doctor in various ways. A very important example is that of homologous serum jaundice which as far as I am aware is only known to occur as a sequel to intravenous injection or withdrawal of blood. It was a long time before we realized that the jaundice which we so happily attributed to the "toxic" effect of novarsenobenzol was not due to the drug, but to the fact that the syringe or needle had not been properly sterilized and that with the injection of the drug the patient also received a minute dose of blood left in the syringe from a previously injected patient. It is not so very long ago that Semmelweiss showed how puerperal fever was carried by the obstetrician's hands. No doubt we are all now well aware of such dramatic possibilities, but I sometimes wonder whether we may not still be helping to spread infection. For instance Ridley (1958) has described the contamination of eye-drop bottles with bacteria and Phillips (1960) mentions epidemics of kerato-conjunctivitis spread by drop bottles.

Finally I would draw your attention to psychological illnesses that may be caused by the way the doctor either handles or talks to his patient. During the war it was not uncommon to see young men who had developed the symptoms of the effort syndrome a few weeks after being rejected for military service without their being told the reason. This was especially so if during the examination they thought that any special attention had been paid to auscultation of the heart. Many an anxiety state is induced too by the facile statements made to patients by well meaning doctors to the effect that they have a "touch of high blood pressure". The patient ignores the significance of the "touch" which is meant to be reassuring but the fear of the high blood pressure fairly soon gives rise to headache, giddiness and palpitations, so often considered by patients and also sometimes by doctors as the typical manifestation of high blood pressure. Whether or not there is such a "disease" as high blood pressure, there is little doubt that very many patients suffer not from their abnormal cardiovascular responses but from being told by a doctor that their blood pressure is high. So too tragedy may follow the faulty handling of patients with coronary artery disease or its incorrect diagnosis. Many years of needless invalidism or even worse may be caused in this way. A good example is the patient described by William Evans (1959). A man aged 47 was diagnosed as having a myocardial infarction and treated by six weeks rest in bed and further convalescence. At the end of this time his employers refused to take him back as a bus driver and try as he would he could not obtain work. He became more and more depressed and finally committed suicide by drowning. The necropsy performed for the coroner revealed widely patent coronary arteries and a healthy myocardium. We should therefore always remember when talking to patients the possibility of inducing an anxiety state by an incautious or injudicious statement and be as careful over what we tell a patient about his symptoms as we should be in prescribing potentially harmful drugs for possibly trivial symptoms.

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RESTORATIVE RESECTION OF THE RECTUM—ITS HISTORY AND PRESENT STATUS*

BY

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The question of cancer and its cure is exercising many minds, both medical and lay. Speaking in most general terms, the rectum is one of the more favourable sites for carcinoma. This is largely owing to the inherent nature of the pathology of rectal cancer—the nature of its cellular division as compared for instance with that occurring in the stomach, and its accessibility to medical treatment. The rectum is a site where the principles of cancer surgery can be applied without difficulty; these are excision, *in one piece*, of (i) the growth, (ii) the organ in which it is arising, and (iii) the field of lymphatic drainage. But in this particular case the patient is left with a permanent colostomy.

Dr. Cuthbert Dukes (1958) whose work on the pathology of this condition is well-known, has pointed out that in early cases (with the disease confined to the bowel wall and with no spread beyond) the five-year expectation of life is 81·2 per cent. He points out that after making allowances for intercurrent deaths from other causes the corrected five-year survival rate rises to 97·7 per cent. Surely if we make any further advances it would almost seem as though the development of a carcinoma and its early and satisfactory treatment would be an insurance in favour of a few extra years, over and above those normally allotted to us!

To many, a permanent colostomy may seem a high price to pay for the hope of cure. A patient faced with this possibility, even though acquainted with all the true facts, cannot but be filled with understandable dismay. His natural abhorrence of an artificial opening in the bowel quite often results in the understandibly plaintive cry—"Is there *no* alternative"?

There are some surgeons who, in their earnest desire for the best radical treatment, tend to belittle the burden to be borne by the patient with a colostomy, and who consider that the sufferer, not having specialized knowledge, is in no position to judge the rights and wrongs of the case. In the final analysis this is of course true, and recognition of such a fact places a heavy responsibility on the surgeon. He must not be blind to the unpleasant disabilities attendant upon a colostomy, with all its inconveniences and potential accidents—accidents so shocking as, in the words of Kipling, "To milk the heart of a man, and shame him before his kind". The surgeon must weigh fully the maximum chances of eradicating the disease against the recognized disability of a colostomy. He must, in addition, make allowances for the average expectation of life of the patient. The surgeon may even have to consider the wisdom of a colostomy in the light of other disabilities; I once had to deal with a man who was not only blind, but had lost the use of his right arm. Therefore, although to strive to eradicate the disease and to leave a naturally continent patient is a worthy aim, it must be stated that many eminent authorities consider the hopes of cure and of sphincter preservation to be incompatible. Nevertheless, operations on the rectum with functional preservation of the sphincters might be said to have arrived—not

*Part of a paper delivered to the Bristol Medico-Chirurgical Society on 13th January 1960.

with a bang—but rather like a train groping its way through the fog to Temple Meads Station. It is interesting to speculate why such operations were so slow to be accepted.

HISTORY OF OPERATIONS FOR RECTAL CANCER

In the earlier attempts at operation for rectal cancer, the attack was made from the perineum with ablation of the lower rectum and anal canal, leaving the patient with a fistulous track to the outside through the granulation tissue. Later, attention was directed towards restoring continuity of the bowel by end-to-end suture after a cuff excision of the growth. The approach was a posterior one with excision of the coccyx and varying amounts of the lower sacrum. This became known as the classical Kraske operation, although there followed numerous modifications, mainly based upon the amount and shape of the excised sacral segment. These operations were disappointing, not only because of failure to cure, but because of the morbidity so often following a breakdown of the suture from tension of the upper segment and subsequent purulent fistula formation. Nevertheless some encouraging experience with this operation caused Grey Turner (1926) to be sympathetic towards sphincter-saving operations. During a discussion at the Royal Society of Medicine in 1948, he stated that seven out of fourteen patients had survived for over five years. The accounts of these seven patients make intriguing reading, for the majority seemed to be alive at that time, from eight to twenty-six years after the operation.

In the early days the failure of the Kraske operation led to attempts at establishing a terminal colostomy in the sacral region, and efforts were made to improve continence either by inserting a variety of bungs or stoppers, or by passing the colostomy through the fibres of the gluteus maximus or lumbar muscles. However it was soon found that these efforts failed, and it was better to have an incontinent abdominal colostomy than a doubtfully continent one in the sacral or lumbar regions. With the advancing safety of intraperitoneal surgery and an appreciation of the importance of the upward lymphatic spread, greater lengths of rectum and lower colon were excised by the perineal route after a preliminary left iliac loop colostomy had been established. This became the popular perineal excision, as advocated by Lockhart Mummery, an operation seldom done now, although in the elderly and infirm it might still be considered advisable. Its disadvantage was the restricted excision of the lymphatic field, but in addition convalescence was often prolonged because of the slow healing of the granulating perineal wound and the occasional persistent mucous fistula; and colicky pains occurred years later, owing to inspissation of cellular débris in the blind loop below the colostomy.

In 1908 Ernest Miles introduced his abdomino-perineal excision, leaving the patient with a permanent terminal iliac colostomy. The operation was based upon study of the lymphatic spread, and on experience of recurrences in the pelvis and perineum in patients treated by the earlier types of operation. Miles was a master craftsman, and a virile exponent of his views. He trained a long and loyal line of assistants who champion his operation to this day. With its 50 per cent over-all 5-year cure, this operation has become the yardstick by which all other forms of therapy are judged. The perineo-abdominal excision as advocated by Gabriel (1934) and practised also by Grey Turner, is in essence the same operation in reverse. But for the objection that it required multiple repositioning of the patient during the operation, it was based, to my mind, on sound arguments, and it has surprised me that it was never more popular. Perhaps it was the lack of euphony in its name that lost it some of its would-be adherents! However, with the exception of a few staunch adherents to each of these operations, the question was resolved, in about 1939, by the introduction by Lloyd-Davies and his colleagues of the "synchronous-combined operation", in which two surgeons worked simultaneously, one attacking the perineum and the other the abdomen. It is not the purpose of this paper to go into the merits and demerits of this operation, but there is little doubt that its major advantage over all previous procedures is

the increased facility it offers when dealing with growths on the border line of operability. Its major disadvantage is the divided responsibility it entails. If the ureter is cut, which surgeon is to blame? It has, however, become the standard operation in most clinics. It leaves the patient with a terminal colostomy, and is based, as was the original Miles operation, upon the lymphatic drainage of the rectum as judged by the carcinomatous spread in advanced or recurrent cases. The diagram originally appearing in Miles's book has been printed in nearly all subsequent works on the subject. This shows the three major lines of lymphatic spread, namely upwards along the inferior mesenteric vessels, laterally over the levator ani muscles to the iliac vessels, and downwards to the perineum and eventually the superficial inguinal lymph nodes. It was this lateral and downward spread which led Miles to advocate, not only ablation of the anus and anal canal, but as wide as possible an excision of peri-anal skin, the levatores ani, and soft parts. Nevertheless, Westhues (1930) in Germany, after extensive studies, has shown that lateral and downward spread only occurs when the lymphatics running upwards to the pre-aortic nodes *are blocked by growth*. This work was published again in 1934, and credit must be given to Pannett (1935) for bringing it to the notice of British surgeons.

RESTORATIVE RESECTION

About this time Pannett, Grey Turner, and a few others commenced to practise excision of rectal growths with reconstitution of the bowel by anastomosis of the colon to the lower rectal stump; first by abdominal and sacral approach, and later by the abdominal approach alone, now known as "anterior abdominal resection". It must be emphasised that this was not a resurrection of the old cuff resections of Kraske, but an operation directed towards a cure by resection of an adequate length of colon and the adjacent upward lymphatic field. Although at times this operation is done in advanced cases as a palliative measure (and should, in fact, be always considered) it was originally designed as a curative operation and did not deserve the name "conservative resection" by which it is often called. American surgeons refer to such operations as "sphincter-saving", or "resection with conservation of the sphincters", although such terms are not strictly accurate, for they would include the Hartmann's operation, which is not intended. "Restorative resection" is the most desirable term, and one which is now widely used in Britain.

Pannett based his operation on the pathological findings of Westhues, and argued that preservation of the levators and the anal canal was justified, because either the case was curable in that the lymphatic spread upwards had not yet become blocked, or the way was already blocked and the case already incurable—in which case there was no point in undertaking a mutilating operation by removal of the lower rectum, anal canal, and sphincters. However, this argument was not widely acceptable and the operation did not at first achieve general adoption. There are, I believe, numerous reasons for this. Firstly, the dominating personality of the brilliant surgeon Ernest Miles coloured most thought where rectal cancer was under consideration. Secondly, there was a wide misunderstanding of the arguments upon which the restoration was based, hence its inaccurate labelling as "conservative resection". Thirdly the technical difficulties of the operation were greater than those of the quick total ablation in the more standard operations. There were also the theoretical fears of insufficient viability of the rectal stump to permit of suturing; the fear of pelvic cellulitis; the possibilities of fistula formation, disruption of the anastomosis, peritonitis, and stricture formation. Although such hazards are mainly theoretical, they were, and still are, thought to be so great as to warrant a preliminary colostomy, or at least a simultaneous colostomy at the time of operation. This necessity for staging the operations is used by some as a strong argument against such procedures. However, in actual practice, such hazards have been found to be largely theoretical, and with the advent of the slowly absorbed sulpha drugs and the antibiotics the procedure of anterior abdominal resection has

become relatively safe, even without preliminary or simultaneous colostomy. Th fact the Pannett was undertaking such resections without colostomy before the day of sulphonamides or antibiotics is a high tribute to his surgical skill. Fistula formatio does occur, but is seldom serious, and can be largely avoided by attention to details o technique. Disruption of the proximal colon due to tension is obviously the resul of faulty surgery, but is likely to occur in the short, fat patient. Since it has been show that paracolic lymph nodes only become involved proximally when the main lymp channels are blocked, it is advisable, when the colon appears to be short, to lengthe it by division of the first sigmoid or left colic vessels within the vascular arch and to leav the arcades intact to nourish the bowel. This marginal step, associated with mobiliza tion of the splenic flexure, will nearly always result in a sufficient length of colon bein available. In advanced cases where lymph spread upwards is extensive a "flush tie" of the inferior mesenteric artery on the aorta is advisable. Even then it may be foun that the descending colon is viable in about 50 per cent of cases (Goligher 1949) and if it is not, it may be possible to bring down the left half of the transverse colo to complete the reconstruction.

The post-operative convalescence after abdominal restorative resection is surpris ingly smooth as compared with the more standard operations, and the immediat shock is appreciably less. There would appear to be much less chance of post-opera tive bladder troubles, probably because the bladder is prevented from falling backward by the new "rectum".

However, restorative resection was not to win a place of honour without som further struggles. Recurrences of growth were reported to occur on or near the sutur line—mainly due, it is thought, to spill and implantation of cancer cells. This ha been largely overcome by refinements in technique. Loss of rectal sensibility an associated incontinence were also reported if too little rectum had been left. At abou the same time, doubt began to be cast upon the validity of Westhues's work whe applied to growths situated in the lower rectum, it being felt that lateral spread ov the levator ani muscles may occur earlier than was originally thought. These tw factors have led to a more careful selection of cases. Curative anterior resection i now reserved for growths occurring not less than 10 cms. from the anal verge, above th peritoneal reflection, and showing no gross local spread. Preliminary biopsy shoul also have shown the growth to be of low or average malignancy. Anterior resectio also has a great place in palliation when there are obvious secondaries in the liver o elsewhere.

RESULTS

Although not universally accepted, restorative resection has been practised no for a sufficient number of years for large centres to be in a position to make a stati stical assessment of it as compared with other forms of treatment. Recent surviva statistics compiled by Naunton Morgan (1957) at St. Mark's Hospital shows a 54 pe cent over-all five-year survival rate, which is slightly higher than for similar case treated without restoration, for which cases the figure was 46 per cent. Workers fro other centres have given rather similar results. It is, of course, tempting to attribut the slightly higher figure to more careful selection of cases, restorative resection bein practised for earlier and more suitable cases. In comparing results it must not b overlooked that the formation of a colostomy itself has a certain mortality attached t it, which cannot be disregarded in long-term follow-up. Perforation and death hav been known to occur from injudicious wash-out; and even suicide within the firs few weeks is not unknown. Lateral space obstruction is a well recognized hazard, a is small bowel obstruction due to adhesions of loops at the sites where the colostom is made.

Incidentally, wider familiarity with this operation has led to its extended use fo diverticulitis coli and endometriosis, and other non-specific granulomata. Provide

the operation of restorative resection is reserved for the right type of patient, it would seem that it offers a chance of survival at least equal to that of an operation involving a permanent colostomy.

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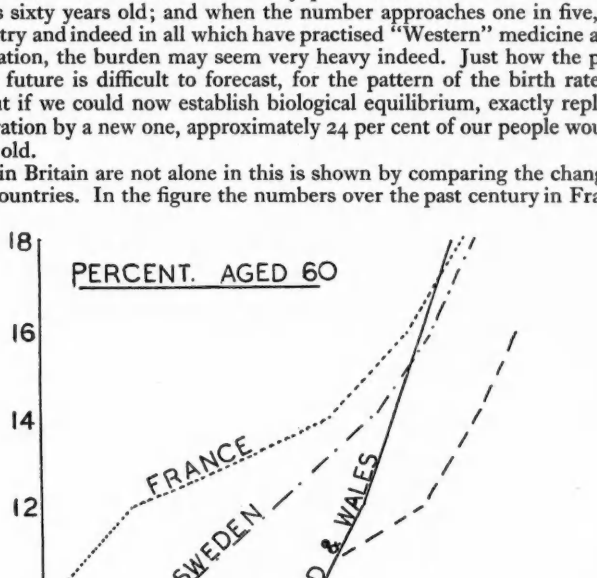
THE GERIATRIC SERVICE

BY

T. W. LLOYD

It has become necessary to revise the medical and welfare services for the elderly because of the stark facts of change in the world's population. Whereas care for the elderly is not a serious problem in communities having no more than two or three per cent of old people, once that figure rises beyond a certain level the burden becomes a very different matter. Respect and reverence for the aged, such as is traditional in the Chinese and Indian cultures is hardly practicable when more than one person in twenty is sixty years old; and when the number approaches one in five, as it does in this country and indeed in all which have practised "Western" medicine and "Western" civilization, the burden may seem very heavy indeed. Just how the picture will vary in the future is difficult to forecast, for the pattern of the birth rate is unpredictable, but if we could now establish biological equilibrium, exactly replacing each dying generation by a new one, approximately 24 per cent of our people would be over sixty years old.

That we in Britain are not alone in this is shown by comparing the change in other European countries. In the figure the numbers over the past century in France, Italy



and Sweden are compared with those for England and Wales, and each country is seen to be experiencing the same trend. Many people seem to suppose that the larg

increase in the number of old people about today is due to the effect of clinical medicine on the preservation of people already old, but life tables show that this change is due far more to increased expectation of life among young people than in the middle aged or elderly. In the U.S.A. life expectancy at birth has increased from 40 years in 1850 to 50 in 1900, 60 in 1930 and 70 today. Similar figures obtain in this country. In contrast to this dramatic increase of 20 years over half a century, the expectation of life of a man or woman already aged 60 has increased only two and a quarter years in the same period. This comparison shows that our increasing number of elderly people is due rather to the control of killing disease in youth, and perhaps in middle age, than to "medicated survival" of the elderly. It is indeed the case that the proportion of truly long-lived people, the nonagenarians, so many of whom remain vigorous to a remarkable degree, is no higher today than a hundred years ago.

What is the startling fact and the basis for a new look at old age is summed up in these figures: Great Britain had one million people over 64 years of age in 1851, five million in 1947 and is likely to have eight million by 1977. Every practitioner who had pre-war experience must have felt the impact of this change—that is why I have thought it necessary to examine the reason for the geriatric service before looking at the thing itself. I do not wish to seem sentimental about "the Old Folks"; the plain statistical fact is that there are far more of them than there used to be and they cannot be dealt with on the same basis as in the past.

This fact established, one must add that the treatment of the elderly sick does not need justification on statistical grounds. Old people need and deserve something better than the care they were offered under the old dual hospital system. Pressure on beds in acute medical and surgical wards led to the too early transfer of many old people to the chronic sick wards of the Poor Law Infirmary where the services needed to ensure maximum recovery were virtually never available. Unless these wards were exceptionally well staffed, they became too easily repositories in which those whose recovery was slow and problematical rapidly lost any chance they may have had. The reputation of such places was therefore not good and difficulties were aggravated by the reluctance of many families to permit their elderly sick to go to "the Workhouse Infirmary". In this desperate struggle many parents lost at the same time the affection of their children and their hope of rehabilitation.

It must be the first object of any geriatric service to provide Time as well as Care; time in which the patient can slowly regain strength and resources for a resumption of the burden of living, time and space in which everything possible can be done to prevent her becoming one of "The Chronic Sick". It is our function to open as wide a gap as possible between failing strength or acute illness and that final classification, and it is a little depressing sometimes to find how few doctors in general or consulting practice appreciate this function. To be asked to take a "Chronic Sick" patient as though we were but middlemen on the road to that final consumer, the undertaker, is not necessarily a stimulating experience.

What the Geriatric Service likes is to be offered the chance of maintaining the sufferer from permanent or progressive disabling disease in a state of maximum activity and happiness, preferably at home; to teach the patient how to live "within the limits of her disability but to the hilt of her capacity" (Rusk 1959). For this, early reference of the case is desirable, not a late and hopeless appeal for a "Chronic Sick" bed.

I have already stressed the need for time. Time alone, with intelligent nursing care, can result in remarkable recoveries. Early this year a woman of 92 came into my care following a myocardial infarct and pneumonia. She was utterly tired of life, so frail and feeble, so despairing that it seemed impossible to hope for recovery. Yet one day, 10 weeks after her illness began I noticed her chatting volubly with an old acquaintance and from that moment a rapid and complete recovery followed.

But time is seldom so effective of itself. Rather has it to be used effectively, first to correct chemical imbalance, circulatory failure, malnutrition, infection in urine or lungs, and later by positive re-training to educate the patient back to the fullest possible mobility. This can be done most effectively only if the patient is first admitted to a hospital unit fully equipped to bring modern medical facilities into play as they may be needed. One such unit per geriatric service will normally suffice and should contain 20 per cent of the total number of beds. Though roughly equal numbers for the two sexes may be necessary in the assessment unit, nearly three times as many long-stay beds will be needed for women as for men, fewer of whom suffer from chronic infirmity. I will not weary you with figures of beds available here except to let you who work in this area know that their distribution in small parcels in seven hospitals in the Gloucester and four in the Cheltenham group is awkward and inefficient. The great drawback to having many small places is that one cannot visit them often, so they can only be used as long-stay repositories in the main. In the interest of the nurses one must introduce some variety into the sort of case under their care; one must remind them that discharge from their hospital is a possibility; but it is not in the interest of the patients that anyone should go direct into a local long-stay hospital who might benefit from the stronger medical staffing which should prevail in the central assessment unit. It is a generally accepted belief in geriatrics that better results come from increasing the central unit until it reaches the optimal size rather than from adding beds to outlying long-stay hospitals. The essence of the modern method is to seek by early accurate diagnosis and effective treatment to limit the number of patients who require long-stay hospital care. At the same time we recognize that in rural communities the possession of conveniently placed long-stay hospitals is a great boon to families and friends.

The service throughout the country though very varied has other accepted general principles. One of these is that one individual should have responsibility for an area, in most cases a consultant physician. There has been no school of training for geriatrics but the field itself, and men from a remarkable diversity of professional backgrounds have made notably successful contributions to its practice. It is clear that what old people need is attention to their disease and a sympathetic appraisal of the possibility of their recovery, combined with the resources to exploit that possibility wherever it is found to exist.

SOCIAL ASPECTS

I find the social background to geriatric medicine wholly fascinating. The different ways in which families react to the illness of parents continually bring surprise. The mutual tolerance which is established by some is a very different matter from the mutual dependence one sees in other relationships whether the partners are parent and daughter, sisters, or husband and wife. Illness may bring a disruptive or cohesive force to such relationships and it is important to know with which one is dealing. Prompt admission may be all-important in handling sickness in one case if the social unit is to have any chance of survival, yet in another admission to hospital may be genuinely dangerous to a social symbiosis which is built on mutual dependence. Often enough there may be some question as to whether the mother or the daughter, the dependent or the prop, stands most in need of treatment. Such situations are especially prone to develop when the illness of the mother coincides with the daughter's climacteric. In the presence of children embarrassment may become even more acute.

Many geriatric physicians feel that they cannot appraise the social situation at second hand, and make it a practice to visit all patients in their homes before admission. Others depute this matter to an Almoner or Local Authority Health Visitor, holding that to do the work themselves is an unprofitable waste of time. I use both methods and find great value in the visits I do myself for they give me an accurate picture of social unit of which my patient is a part.

I do not subscribe to the view that the bond of dutiful feeling between relations is much less strong than it used to be, but with the increasing numbers and proportion of elderly people one must recognize that this feeling needs support. Only if the relatives are able to resume the care of the patient can we achieve our object of restoring her to her place in society, and there certainly are many situations in which the onset of illness in the old person may be hailed as an opportunity to shrug off the burden of social strain for ever. Early contact between geriatric physician and family may put this matter in true perspective on both sides. While the physician will feel that his patient has social rights *vis-a-vis* the family that must be supported, and must consider the most profitable use of his beds in the service of the community, he must also recognize the implications and effect of the situation on the family or other social support. It is essential, especially in the three generation family, to see that the social rights of the disabled grandparent are not always given priority over those of the children and grandchildren.

Much use can and should be made of the geriatric beds for supporting the family. In my unit we run a limited service of this kind, some sixty men and women are being taken in during the summer months this year for periods of two or three weeks to enable the family to go on pre-arranged holidays. We have to be inflexible in these arrangements and it is often desirable that one of the hospital staff should see the relatives or visit the home in advance to decide whether any form of treatment can be attempted simultaneously with the custodial care, and whether a longer stay should be planned with this in view. Nevertheless from time to time the best laid plans go wrong. Isaacs and Thompson (1960) have reported that of forty-six such admissions only twenty-six patients returned home on time, six died, two went to Welfare Homes, twelve stayed longer than planned. I think this is too high a figure of failure and have had much better success myself, but one does in this way come across patients who can benefit from longer periods of treatment. We do of course give periods of relief at other times than the summer holiday if the indication is sufficient.

There are other forms of support which the hospital service can give. DeLargy (1957) believes in the value of regular, rhythmic relief to relatives, and has set aside a ward into which he admits patients for six weeks after intervals of six weeks; six weeks in, six weeks out. He reckons that thereby he gets two patients into each bed over the year yet sustains their feeling of social importance. He claims also that someone is always looking forward happily to something; either the mother to her return home or the daughter to the impending spell of relief! Few of us can emulate DeLargy exactly but recurrent admissions at more or less regular intervals may be the kind of support which will prevent a family from getting exhausted to the point at which they want at all costs to be rid of their incubus.

DIAGNOSIS

It may seem impertinent to tell an audience of doctors that diagnosis is an important step toward sucessful treatment. I do so only because it has so often been allowed to go by default in chronic sick wards. In most new geriatric services examination of these people yields a rich harvest of remediable conditions and in many practices patients are to be found who might benefit from a fresh appraisal.

Once a patient has acquired a label in one's mind it is easy to accept implications that are not always justifiable. A patient with hemiplegia, especially if this is accompanied by dysarthria or aphasia, may suffer through ignorance of the possibilities of rehabilitation, or just from lack of a clinical review from an unjustified degree of incapacity. Twice recently I have admitted such patients to relieve strain on their family supports and have found that a very material improvement in mobility and aptitude could be achieved when a proper attempt was made, to the great benefit of both patient and family. If the possibility of rehabilitation is constantly borne in

mind surprising results may be achieved. Some people become vastly more efficient if they can use hearing aids or if ophthalmic treatment is possible. It is incumbent on *someone* in each case to think of the possibility.

Senile dementia is a very dangerous label for it denies all hope of recovery. Beware of it for it is not such a very common condition. Confused states of mind can, as we all know, derive from such diverse states as chemical imbalance (hypoglycaemia or uraemia), anoxia due to anaemia, carotid and cerebral atherosclerosis or congestive cardiac failure, as well as from personality withdrawal and frank psychosis. Many, perhaps most confusional states are reversible. I have seen more than one so-called senile dementia recover after a course of enemata.

Again if the term exists in your vocabulary strike out "myocardial degeneration". As a clinical term it means almost nothing but ischaemic heart disease with widespread fibrosis. Banish the vague chimera of a senile degenerate myocardium from the mind of the profession and many more cases of malnutrition, dehydration, anaemia and bronchopneumonia will be diagnosed and treated. In frank cardiac disease the clinical concept of myocardial degeneration specific to ageing seems to carry the implication that treatment will fail, whereas it is the case that cardiac failure and disease in old people are no less responsive to treatment than in middle life. Normal heart muscle would seem to be almost immortal!

Cardiac failure must always be regarded as a symptom, not a diagnosis. I have for instance recently had two cases of dropsical failure which responded to opposite approaches. One man with tachycardia and high output failure, warm blue hands and a history of wandering round his village in a strange and frightening way was found to be in a thyrotoxic state though the thyroid gland was not enlarged. When treated with carbimazole he recovered completely. A woman with equally severe dropsy was so tired and lethargic she had no wish to live—the coarse skin, hoarse voice and bitter complaint of the cold weather made the diagnosis of myxoedema obvious, and she recovered well on thyroid treatment. In old age thyroid dysfunction is often atypical in presentation but if one keeps the possibility in mind myxoedema, which is fairly common, will seldom be missed; thyrotoxicosis being quite rare may be less easy to spot.

Coronary thrombosis in old age usually presents without significant pain. It may be that failing memory makes the patient a bad historian, or perhaps it may be due to the increasing collateral system of arteries which develops in late years. Whatever the cause severe cardiac pain is a rare complaint. The unexpected onset of congestive failure, a sudden faintness, even a fall, may be the only indication. Recently a woman aged 68, a known diabetic, came under my care having collapsed the day before and begun to vomit. Vomiting continued for several hours and she was admitted in diabetic coma precipitated by vomiting due to myocardial infarction.

In diagnosis *ab initio* and in continued care we must remember that multiple pathology is almost the rule in old age. More and more often it has been borne in upon me how close an eye must be kept on geriatric patients in the acute assessment ward. Many of them pass through a series of disease states any one of which might carry them off. Whatever the presenting diagnosis there is a risk of bed sores, pneumonia, urinary infection and thrombophlebitis occurring. Till I began to practise geriatrics I never dreamed how common fatal pulmonary infarction could be. Recurrent anaemia due to intestinal haemorrhage is astonishingly common, usually without a demonstrable source. One must keep sharply alert in these wards. Time can help us only if we know what we are up against. Life is certainly easier in acute wards where so many of the patients make one diagnosis do for one admission! The risk of embolic phenomena is much in my mind especially when stroke occurs in the presence of auricular fibrillation. Arterial emboli of every degree are ever present possibilities in such cases and justify to a late age the use of anti-coagulant drugs in cerebral embolism and in myocardial infarction.

Sometimes disease states which have previously been present in mild degree achieve prominence because of social crises. A short time ago I was asked to see an old woman who had taken to her bed with pneumonia and generalized senile tremor. A visit to the house unmasked a severe case of iron deficiency anaemia in the aged husband. This had remained unnoticed because while the wife was able to continue her fairly active life the husband had just sat still most of the day.

In another instance a pair of old ladies lived together, one in effect looking after the other. When the prop came into hospital with a myocardial infarct the other came in as a social necessity and was found to have a profound degree of pernicious anaemia. At the time of their discharge the orginal status of the two women was to a large extent reversed. The dependent one had become physically vigorous whereas the original prop was still in mental outlook an invalid.

In a third case a cerebral thrombosis of minor degree, which incapacitated a vigorous healthy man of 82, threw an intolerable strain on his wife's cardiac reserves and admission of both parties to hospital became an urgent necessity. As is so often the case the man recovered well, long before his wife whose breakdown disclosed a state of fatigue of long standing, congestive cardiac failure and troublesome cervical spondylosis.

REHABILITATION

The third phase of medicine (Rusk, 1959) consists of re-training the patient to the needs of daily life and restoring to normal function the disabled limbs. In old people this can be a difficult, protracted, and often disappointing business, but whenever it can be it should be done. It is easy to say that all the old folks want is to be allowed to rest after their labours, but prolonged bed rest carries very real dangers. Even the period of 6 to 8 weeks immobilization which was once required for fractures of the neck of the femur carries a risk of rapid decalcification of the skeleton, loss of muscle power, of bladder control, even of reason itself, so that this treatment has been described as hanging the patient by the leg till she is dead! (Crockett, 1960). Geriatric physicians live in dread of these consequences of bed rest. Osteoporosis indeed is so common a condition as almost to be a normal accompaniment of old age in women. Any disease process or any treatment involving prolonged bed rest can accelerate its insidious progress and bring about disaster, so it is not surprising that the bedrock of treatment and rehabilitation in the elderly is to get the patient up and dressed. If we feel like human beings we are more likely to behave as such. If for 80 years we have been accustomed to certain standards, preservation of as much normality as possible in daily life will help to maintain *amour propre* and even to restore reason to the confused mind. The normal position of human beings is upright. If the old are confined to bed many of them withdraw from reality and sink back into infantile dependence.

Rehabilitation takes many forms. Care of the feet is of prime importance. One cannot walk on painful feet with any ease. Chiropody should be readily available and I personally make it a practice to conduct physical examination from the feet upwards. If the feet are sound and if suitable footwear or ankle supports are selected it is surprising what obstacles of skeletal deformity or neurological defect can be overcome, provided unnecessary strain is avoided, and in this context I must remind you that obesity is a terrible handicap in old age. The idea of carrying 20, 30, or 50 extra pounds about all day long is one which nobody would entertain if the weight was other than bodily fat. As physical strength decreases gravity may at last become the dominant force. Provision for ageing should take account of this danger.

I should like to illustrate our general attitude to rehabilitation by reference to hemiplegia. It is true for practical purposes that recovery of the arm and hand begins within 3 months or not at all. If little or no recovery occurs in this period it is wise to concentrate effort on teaching the patient to use the other hand comprehensively.

The paralytic leg on the contrary may become a useful member later than this an we do not despair of recovery till 6 months or more have passed. From the earlies possible stage we encourage the maintenance of muscle tone in the quadriceps femoris and by passive movements of arm and leg seek to preserve the full range of join movement. Everything possible must be done to prevent "freezing" up, of th shoulder especially, so that such muscular recovery as does occur will not be unneces sarily embarrassed. Usually the leg does better than the arm. Perhaps most suc cases can learn to walk with the help of a stick or a tripod if the cerebral cortex an personality remain sufficiently intact. When there is no recovery of the leg it ca usually still be of some value as a spastic support, but in these cases we must hop for recovery of the arm so that two tripod sticks or a light walking aid, or even crutches will make mobility possible. In short, one must in all cases make the most of suc function as can be preserved.

Aphasia may be a most disabling consequence of cerebral thrombosis and hemian aesthesia makes rehabilitation more difficult. The situation is still worse if homony mous hemianopia is present. But in such cases the dominant factors are first th patient's personality (this is all important), and second the enthusiasm and persistenc of the team which has to be maintained despite repeated disappointment. My ow attitude, which is I think tempered by a reasonable clinical common sense, is tha any degree of independence is worth seeking. If the patient can do no more tha feed himself and write letters, that is really valuable to some people; but if he ca walk, however slowly, he can escape the most profound humiliations.

INTEGRATION OF SERVICES

Care of the elderly is divided between the general practitioner, the hospitals an Local Authority. Once a state of failing independence is reached we must conside whether more help is needed than the family can provide. The Local Authority responsible for maintaining Welfare Homes, Health Visitors, the Home Help Servic District Nursing, Meals on Wheels, Chiropody, etc. The hospital Board is official responsible only for those who need hospital services. In rare instances the geriatr physician is also physician to the Welfare Homes and in such situations traffic betwee Homes and Hospitals moves with great freedom—but this is a very exceptional arrang ment and increasingly it is the vogue to integrate the Geriatric Hospital Servic with that of general medicine. I think this is correct; they are different aspects the same thing. Nevertheless the geriatric physician should be able to guide bot the Welfare Department and the general practitioner so that one provides what the othe needs and both know what services can be made available to people in need.

How far is the Geriatric Service from being a success? I think that few places indee can claim that they have a wholly satisfactory service, and certainly in this clinic area it would be surprising if this were the case. A unified service was only initiate 7 months ago and we are a long way from reaching our peak of efficiency. It probabl is true that a considerable number of patients became "chronics" in the past who toda might be maintained at a reasonable level of independence. But they still occup hospital beds and till they die those beds remain occupied. Gradually however a increase in the speed of turnover and hence in the number of patients admitted an discharged is becoming perceptible. In the last 6 months 501 patients were admitte to the hospitals of my service, compared with 413 in the corresponding period la year. Moreover the relation between death and discharge as the probable consequenc of admission has been reversed.

Deaths,	January—July 1959	216 (52 per cent)
	,, ,, 1960	227 (45 per cent)

More important perhaps to the general practitioner is the fact that there are few patients on the waiting list than there used to be and these get into hospital quicke

In the last 4 months no one has had to wait as long as 4 weeks for a bed and many have been taken in within days of request.

The future value of the service however must lie not in coping with the urgent needs expressed by general practitioners' demands for hospital beds, but in an expansion of the service directed at prevention of decay. Sometimes it is now possible by joint consultation between the general practitioner and geriatric physician so to deploy resources as to maintain people in their homes without admission or with only brief periods of in-patient treatment. Expansion of the Domiciliary Welfare Services will help in this direction. Meals on Wheels is one such service which should be expanded. Friendly, informal visiting, or regular transport to an Old People's Club may make the difference between normal mental alertness and the insiduous onset of personality withdrawal and dementia. Occupational therapy at home may sometimes improve a domestic situation which without it would be intolerable.

A vigorous out-patient service probably can be of real value both to the general practitioner and to the discharged patient. In Oxford especially a Day Hospital which patients attend one, two, or three days each week makes long term rehabilitation possible through occupational therapy and provides much needed relief for the relatives especially of confused patients. We cannot aspire to such luxury as Oxford has but we have started a Day Hospital in a small way in Cheltenham, and such things grow.

Close co-operation with the psychiatrists is mutually valuable. We are setting up a workable arrangement whereby both they and I can admit cases of severe confusion to certain beds in which my psychiatric colleagues and I will examine and assess each patient and ensure that the most suitable treatment and disposal is arranged.

We have a long way to go to reach the standard I seek and time is not on our side—the numbers of old people grow. But I am very sure of one important point. The solution to the problem does not lie in adding more and more chronic sick beds where chronic neglect is the medical routine. It lies rather in the vigorous use of well equipped beds by interested medical men. Geriatrics is not a specialty; it is a technique, and above all it is an attitude of mind which will one day be taught to the medical student and will become an integral part of the attitude of every consultant and every practitioner in general medicine.

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RESEARCH ON RHEUMATIC DISEASES

OR

"WHAT'S COOKIN' AT BATH?"

BY

G. D. KERSLEY, T.D., D.L., M.D., F.R.C.P.

It was within the Royal National Hospital for Rheumatic Diseases that the research unit, whose activities are to be reviewed here, began its existence in 1949. But the hospital had been famous, and had been engaged in research, for many years before that. Before the last war, it was the Mecca of students of rheumatic disesase from all over the world. It is the oldest spa hospital in the world, and was the first to specialize entirely in rheumatic diseases.

The Hospital's history begins with the opening of the subscription list by Beau Nash in 1723. Ralph Allen provided the stone, and John Wood the Elder gave his services as architect, free. In 1742 the hospital was opened for 150 patients from outside the City of Bath, under the name of "The Hospital or Infirmary at Bath", with Dr. Oliver (of Bath Oliver Biscuit fame) as the first physician and Mr. Pierce as the first surgeon. After this, among the subscriptions received one of special interest was of £1,000 from the Guildhall, London, for services to those wounded in the 'Forty-Five rebellion, and one of £29,280 from a Dr. Perry. First, an extra floor containing a pool was built and then in 1861 a complete new wing was added. Before this the patients went to the City "baths", if necessary by sedan chair, but they wore a token of brass to show that they were patients of the Hospital and were not to be served with beer *en route*. In 1887 the Hospital received its Royal Charter from Queen Victoria, and in 1911 His Majesty King Edward VII became Patron. In 1935 it was decided to build a new hospital and His Majesty approved the change of name to the Royal National Hospital for Rheumatic Diseases. In 1939 Her Royal Highness the Duchess of Kent, then our President and now our Patron, visited the Hospital and accepted purses as contributions to the rebuilding fund. In 1942 the west wing received a direct hit in an air raid and was partly destroyed. Under the National Health Service Act of 1946 the funds collected for rebuilding were appropriated into the common pool. Since then every effort has been made, first to obtain permission to build a new hospital as previously planned on the prepared site, and then, when the permission was withheld, to obtain sanction for the proper reconstruction of the old building. Firstly a deputation appealed to the Minister of Health, then a Press Conference in London received phenomenal support, especially from *The Times*, and finally the efforts of an all-party deputation of M.P.s were crowned with success. It is only this year, after 25 years of planning and frustration that the Ministry of Health has sanctioned the "reconditioning" of the hospital, with an extra half-floor, at the expenditure of approximately a quarter of a million pounds. Detailed plans and quantities are now being drawn up and it is hoped to commence the alterations next spring and complete them in about three years' time. After rebuilding, with the preservation of the eighteenth century façade and hall, the hospital will have only a hundred beds, but will then have all "mods. cons." screened beds, properly grouped treatment departments and better intercommunications with proper bed lifts. A new third floor will house a minor operating theatre and a plaster room and we hope new clinical research facilities. It will cease to be the pre-Victorian death-trap in which we have worked for so many years. This hospital

has proved how little bricks and mortar really count. Lord Horder in 1938 stated that it was doing better work in rheumatism than any other in the world, though the building was fit only for rats to live in!

But to return to our subject of research—this of course started long before the National Health Act and the foundation of the Unit. Apart from early contributions on gout, the Royal National Hospital in 1930 led the way in the use of plaster techniques in the splinting of joints and in 1935 a Governor, Mr. Sidney Robinson, paid for a whole-time research worker, Dr. Levinthal, to carry out fundamental work on the immunological conception of rheumatoid arthritis—work which fits in well with some of our newest concepts.

When the Rheumatism Research Unit was founded in 1949 it was designated as belonging to the South West and to the Oxford Regions, though it was always financed by the South West Regional Hospital Board. It grew in perhaps a somewhat untidy fashion financially, but it had a very happy and productive childhood. Clinical work, clinical research, and fundamental research were so closely bound together as to be, at times, almost indistinguishable. Clinical registrars to the unit helped with research, and research fellows of the same status helped with clinical work. As all aspects were financed by the Regional Board with the help of external grants obtained from the Nuffield Foundation, Empire Rheumatism Council, and personal gifts and legacies, everyone was happy. Even though part of the work was carried out in the unused hospital mortuary, keenness and co-operation overcame these difficulties. In 1951 however part of the unit moved to new quarters on the Combe Park Site.

From 1st April 1959, the fundamental research has been taken over by the Medical Research Council with a local Advisory Committee of Directors, consisting of four Professors from Bristol University, three Bath physicians and a member of the Medical Research Council. This has of course given the unit a new status, but it has dropped an "iron curtain" between fundamental and clinical research in all matters of finance. It is however hoped that the barrier will exist only at the level of finance, as all research workers agree that both the scientist and the clinician gain enormously by working in the closest possible physical and psychological contact.

It is difficult to make a readable review of fundamental research and its intricate facts and theories, which are "Greek" except to those recently trained in biochemistry and its methodology. From early beginnings on fibrinolysis and tryptolytic enzymes, the Unit concentrated more on methods of tissue culture and on the *in vitro* changes occurring during tissue growth, its accelerators and inhibitors. Normal and rheumatoid synovial membrane was examined in this way, and various techniques for studying artificially produced arthritis in animals were investigated. Animal work with rats, guinea pigs, and rabbits was carried out on the utilization, excretion, and deposition of gold, using radio-active isotopes, in order to add to knowledge of auro-therapy [8, 16].

The early post-war clinical research carried out at the Royal National Hospital was concerned with the histology of rheumatoid nodules, changes in skeletal muscles, and degenerative changes in tendons leading to their rupture [1, 9, 10, 12]. This was followed by work on dental sepsis in rheumatic disease [11], the use of blood transfusion in rheumatoid arthritis, [21] and a considerable number of observations on pituitary stimulation with insulin hypoglycaemia or E.T.C. and its biochemical consequences [13, 14]. An experiment with a well-known vaccine showed that the psychological effect of the regular injection of the saline control was of no mean value [15]. The anarthritic syndrome of the elderly [16] and an episodic rheumatoid onset often confused with palindromic rheumatism and intermittent hydrarthrosis [1] were described.

Much clinical research consists of clinical trials, in the planning of which a definite discipline has to be followed. The purpose of the trial and the type of case to be admitted must be defined. In some trials where quick results are expected, the patient may act as his own control and the value of different remedies may be compared by a "blind" change in treatment. As a rule, however, control groups selected by random

sampling are essential, and neither the patient nor the assessor should know the drug the patient is taking. Every effort must be made to neutralize possible psychological factors. Statistical analysis of the data is essential. The assessor should be the same for each recording—preferably a research fellow of senior registrar grade—but the over-all welfare of the patients must remain the responsibility of a physician who, on ethical and humanitarian grounds, must be prepared to put the patient before the project and withdraw him from the trial, noting the reason for withdrawal, if he thinks it is to the patient's advantage.

The first major clinical trial was concerned with the effects of radiotherapy [2]. Rheumatic patients in a carefully controlled series were given various dosages of X-ray therapy, and in the control group the patients were laid on a couch without the current being turned on. It was found that those with rheumatoid arthritis received no benefit, about 50 per cent of osteo-arthritics had some temporary amelioration of symptoms, and that 95 per cent of those with ankylosing spondylitis were greatly improved, the benefit lasting in the majority of patients for at least one year. The medium range of dosage, about 1,200 roentgen units, was found the most suitable. This investigation was carried out before the leukaemia dangers of radio-therapy had been discovered, but now the knowledge that radiography increases the chance of developing leukaemia about seventeen-fold must be considered before it is used, especially as it is so frequently required in spondylitics in the comparatively young age groups. However, this treatment still appears justifiable where severe pain cannot be relieved by other methods.

During this same period a second clinical trial was carried out on the use of intra-articular injections in osteo-arthritis. It was found that some slight benefit in the way of increased mobility and reduction of pain was produced to an extent equal to that produced by "novocaine", saline or lactic acid. The control group suffered only needling of the joint.

A considerable amount of work [4, 5, 6, 7] was carried out on the anaemia usually associated with rheumatoid arthritis. It seemed that there were many factors involved —neither deficient absorption, blood loss, changes in iron binding, nor haemodilution could explain the anaemia. Parenteral iron improved a large proportion of patients resistant to iron by mouth. Cobalt assisted in a few resistant cases but gastric complications were frequent. Bone marrow findings were equivocal. It seems probable that deficient iron absorption, excessive iron requirements, and some haemopoietic abnormality all played their part in the anaemia of rheumatoid arthritis. To this may be added the small repeated blood losses due to aspirin treatment, probably insignificant except when long continued in the menstruating woman, whose safety margin is reduced.

Projects still in progress consist of investigation of the uricosuric treatment of gout, an evaluation of antimalarial drugs in rheumatoid arthritis, further work on the treatment of anaemia with iron, and the use of long-acting steroid injections, not yet on the market, in order to determine their dosage, length of action, and likely value when there is the complication of peptic ulceration.

In the antimalarial trial a series of patients suffering from rheumatoid arthritis was given plaquenil, camoquin, and control tablets for alternating periods [1]. A high percentage of patients enjoyed suppression of symptoms with the antimalarials, but the margin between toxicity and therapeutic benefit was very small, and one patient developed agranulocytosis as a result of camoquin treatment. Temporary punctate corneal opacities were common. It was felt that this group of drugs might be used with justification in a limited number of cases where safer, simpler measures are ineffective, provided careful supervision is maintained.

For some three years now a series of fifty patients with gout has been followed up clinically and biochemically while under treatment with a number of drugs which increase uric acid excretion [19, 20]. These consist of aspirin in large doses, probenacid

("benemid"), "longacid" (or "urelim"), "anturan" (G.28.315) and zoxazolamine ("flexin"). Aspirin is cheap, but in large doses it is depressing and is a gastric irritant; "benemid" is satisfactory in about 80 per cent of cases but produces toxic symptoms in the remainder. "Longacid" is very similar in its effect. "Anturan" is more powerful and virtually non-toxic. Zoxazolamine appears to run "anturan" a fairly close second as the uricosuric agent of choice. Apart from aspirin, all these uricosuric agents tend to stir up gouty attacks during the first six weeks of administration, but from thence onwards the attacks become less severe and less frequent, and any interval swelling is reduced. During these first six weeks therefore colchicine should be administered regularly, and butazolidin may be given in addition for two days at a time to control any severe attacks. Aspirin inhibits the effects of the other drugs, but the remainder are complementary to each other. Long-term and regular administration of uricosuric agents is essential to their effectiveness. They appear to have no significant effect on plasma cholesterol levels or prothrombin times, a possible drawback that has been suggested by some cardiologists. Their use has revolutionized the treatment and prognosis of severe gout.

Apart from research work carried out on its own initiative, the Unit has been participating for the past five years in various multi-centre trials organized by the Medical Research Council, Empire Rheumatism Council, and Nuffield Foundation. Some five to ten centres in the country may work on the same project, using the same criteria laid down by a central committee, and the results are assessed by one medical statistician. The first trial showed that in the long run little more benefit was to be expected from cortisone than from aspirin[22]. Prednisolone however produced considerable long-term benefit including less deterioration as seen on consecutive X-rays [23]. Gold therapy produce definite amelioration at the end of a year's follow-up, when the effects of a course of 1 gm. was compared with that of 0·01 mgm. [24]. These trials are still being continued to assess long-term results and toxic reactions.

As we said before, with the change in ownership of the unit a temporary iron curtain was dropped between the fundamental and clinical research. A chink in this curtain is beginning to appear in that clinical research facilities may be available in the rebuilt hospital, and the Medical Research Council may help with some of these, thus bringing such projects under the aegis of the Committee of Directors of the Unit. Likewise one day the unit's fundamental work may move back to its original home at the Royal National Hospital, so that once again it may stimulate the clinicians, and the latter in their turn may help the unit to keep its feet firmly planted on the ground, for in spite of recent theories on parthenogenesis, intercourse between the research worker and the clinician is still essential for productivity.

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CHRONIC OSTEOMYELITIS WITH MATURATION ARREST OF GRANULOCYTES

(A Clinico-Pathological Conference of the University of Bristol Medical School) on 25th October, 1960, P.M. 6571.

CHAIRMAN: PROFESSOR T. F. HEWER

Mr. J. W. E. Snawdon: This patient was first seen by me on the 18th August 1959, but I think I should mention that he had been a patient at the Dental Hospital for quite a few years. I have his record card here from which I see he first came under their wing in 1953, so we know that for several years he was an apparently normal patient and had routine conservative dentistry. I think in 1953 he came with a rather neglected oral condition and was persuaded to take an interest in his dentition. He seems to have looked after it reasonably well according to the notes, right up to 1956. At the end of 1956 there is the last entry of any treatment other than the happenings in July 1959. He came up in 1959 with some pain, localized in the left maxilla and swelling, and he was seen as an emergency. It was recommended that his left upper molar should be removed and this was done under local anaesthesia. Nothing was heard of him then, that is from the 7th July when the tooth was removed until the 14th August when he came back again complaining of an unpleasant smell and bad taste in his mouth. He was not feeling particularly well and the resident who saw him at that time noted that a large piece of maxilla was sequestrating and he had possible sinusitis. He was seen again on the 18th August, roughly 5 weeks from the time of the extraction of the tooth in question and on that occasion the patient was referred to me.

The thing that struck me about this man when I saw him was that he was an obviously ill patient. He was very pale and his temperature at that time was not raised at all, but he obviously looked ill and should not be going about in the normal way, working, as he was at that time. When I examined his mouth I saw some bare bone in the left maxilla, but no purulent discharge of note, it was in fact relatively dry, apart from a certain amount of serious exudate on the margins. He had an oro-antral fistula at that stage and a sinus x-ray which was taken showed an opacity of the antral cavity on that side. The main point was that this was obviously an ill patient and the thing we promptly did was to get him admitted to Hospital, and having got him admitted I asked if Professor Perry would be so kind as to see him. At the time however Professor Perry was away and Dr. Leather very kindly came in and had a look at him and carried out the necessary general investigations in the ward. So far as the jaw was concerned we felt there was very little to be done. In general a sequestrum will sort itself out and either present a picture which requires surgical intervention or separate itself spontaneously as often happens. The oro-antral fistula would not present any unsurmountable difficulty subsequently. Now the main point about this man was that he was an obviously ill patient and we felt that the jaw was really a secondary consideration at the time I first saw him. He was investigated and the abnormal blood picture, about which Dr. Leather will have something to say, was discovered. All along we felt that here was the problem which was basically the chief one, an ill patient with this abnormal blood picture where we felt that any surgical treatment of the jaw was contra-indicated and it would not be in his interest to do anything to attempt to remove the dead bone. We felt that the jaw problem then was undoubtedly secondary to his systemic condition. In other words that he had this condition present when the

tooth was extracted and the tissues reacted in this way because of the nature of hi blood condition at that time. There is one other point I would just like to clear up and that is to say he improved a lot on his general treatment. This went on fro August 1959 until December 1959, when he was not quite as good but on the whol was much the same as in the early stages; I was always expecting that as his gener condition improved the piece of bone would sequestrate, but on the 19th January 196 he came in and said he had come prior to the next routine check that had been arrange because he was getting some discomfort in his upper jaw and also some more offensiv discharge. He was obviously looking very bad, he had quite a lot of boils around hi face, he looked very pale again and obviously ill, so I wrote to Professor Perry a follows "This mutual patient of ours came to see me to-day. I do not feel very happ about his condition, his pallor has increased again since I saw him six weeks ago an he is being troubled by an offensive nasal discharge. The amount of necrotic bon visible in the mouth has increased and the oro-antral fistula is of course still present Whilst I feel that any surgical intervention is at present contra-indicated in this case wonder how you now regard his general medical condition also the possibility of re moving the necrotic bone some time in the future? I think if left to its own devices will separate but it is likely to prove rather troublesome to him." And Professor Perr in his reply said "We saw this patient at the end of December, his haemoglobin wa then just under 70 per cent. If he is getting worse perhaps we should have him int hospital again and we would ask your advice when he is in".

That time when I saw him in January was, in fact, the last time that I actuall examined him and the next thing I knew was the post mortem findings.

Dr. H. M. Leather: You have heard quite a lot about this patient already and shall not emphasize any of the dental aspects of his illness. He was a man 60 years age, and was a goods porter. In the previous history he had had a prolapsed inte vertebral disc in 1952 for which a laminectomy was performed, and after a certai amount of subsequent pain at that period the trouble cleared up and did not retur He had had an attack of bronchitis two years before his present admission.

In March of last year, three months before the tooth socket trouble he attende the Casualty department with a septic finger. He was given some glycerine an mag. sulph. paste and also given an injection of 1 mega of crystalline penicillin. Follow ing this he fainted. He was accordingly detained in Casualty for an hour or so befo being allowed to leave. There were no sequelae to this curious episode, he develope no skin rashes, and in retrospect we were inclined to think that this was a faint th might have followed any injection. We first saw him in August 1959, Mr. Snawdo having referred him. He told us that he had lost several pounds in weight over rece months but that was the only addition to the recent history. He looked ill, the mucou membranes were pale, the spleen was impalpable, the lymph glands did not appear t be enlarged, and there were no petechiae. Hess's test was positive. A blood count w done and revealed haemoglobin 58 per cent, the red blood cells showed considerab anisocytosis with some macrocytes present. There was generalized hypochromi Total white cell count was 3,200/c.mm. and only 680 of these were polymorphs. Th platelet count was 120,000/c.mm and the sedimentation rate was 44 mm. in the fir hour. These findings, with a decrease in the red blood cells, white blood cells an platelets, suggested we were dealing with a marrow hypoplasia and accordingly sternal marrow was carried out by Dr. Raper. This showed that the degree of cellu larity in the specimen examined was normal and that only slight changes in the myeloi series were present. Dr. Raper felt that this marrow picture might have represente recovery from a hypoplastic phase. Now hypoplasia and aplasia of the bone marro may result from toxicity to a variety of substances. Among the many drugs which ca do this are the heavy metals such as gold and mercury, the antibiotic chloramphenica the sulphonamides, thiouracil and its derivatives, tridione and various substances us in industry. The number of drugs which can do this is increasing all the time. Th

patient was questioned very closely to determine whether in fact any such drug had been given but there was no evidence that he had taken anything that might have caused hypoplasia of his marrow.

We took a culture from the tooth socket to see if there were any pathogenic organisms present; we did not think it very likely that there would be, and in fact we grew a mixed flora with alpha haemolytic streptococci predominating, as one might expect from the mouth. We gave him a course of tetracycline, on the assumption that by giving him a wide-spectrum antibiotic we might improve the condition of his tooth socket, but it had little effect except that his temperature, which had been a little raised to 99° on admission, settled during that course.

We also gave him a blood transfusion, 3 pints of blood in all, which improved his haemoglobin level. When the blood was grouped it was found that it was rather difficult to determine which group it was. It appeared that it might have been group O or A. In fact it was concluded that it was probably group A but this difficulty with the grouping raised the possibility that we might here be dealing with aleukaemic leukaemia rather than an ordinary marrow hypoplasia. He went home after a month and his condition was pretty well unchanged. The haemoglobin had risen to 83 per cent following the blood transfusion but the tooth socket remained more or less the same. The white count had remained very low, the lowest level recorded being a total of 1240 white cells/c.mm. with only 140 polymorphs. He said he felt better however and he certainly had gained a little weight.

He was seen a couple of weeks later in Outpatients and at that time his condition was more or less the same, but he said that on two occasions some brown fluid had come down his left nostril. It was thin watery fluid, and there had been a few cc. on each occasion. We attributed this to antral involvement which would not be surprising as the tooth socket affected was in the left upper jaw. In fact as Mr. Snawdon has told you there was an oro-antral fistula present. There was no clinical evidence of any acute process going on, there was no tenderness over the antrum and we did not do anything about this discharge.

About 7 weeks after that, in November of last year, he was re-admitted with a boil on his cheek, and also quite a severe blepharitis. The physical signs at this time were more or less the same, the tooth socket being pretty well unchanged. We took a swab of the conjunctiva and grew a *Staph. aureus* which was fully sensitive. The blood count was substantially unaltered and another bone marrow biopsy showed very little change from the first. On this occasion also we gave him a course of tetracycline and we tried to prevent further staphylococcal infection by giving him neomycin cream to put up his nose and hexachlorophene dusting powder for the perineum, both sites well known to be areas of staphylococcal proliferation. He also had hexachlorophene in the bath water for the same purpose. The lesions resolved and he went home.

On the 19th January he was seen by Mr. Snawdon and was subsequently admitted under the care of Dr. Barritt at Ham Green Hospital in March. His general condition was again pretty well unchanged. He complained of some pain over the left side of the back of the head and there were some glands in the posterior triangles which were thought to be enlarged, though not painful. Well, once more the bone marrow was examined. There were again relatively slight differences about which we shall hear, but they did raise the possibility that this might be myelomatosis and so his urine was examined for Bence-Jones protein and his serum proteins were electrophoresed to see if there was any of the abnormal myeloma protein present. In fact there was no Bence-Jones in the urine and though the plasma proteins did show a slight rise in the gamma globulin there was no abnormality other than that. He was again given a blood transfusion of 2 pints of packed cells, and a course of tetracycline followed by a course of erythromycin. He was also (I think on Mr. Snawdon's recommendation) given hibitane lozenges to suck. The blood transfusion raised the haemoglobin level from 60 per cent on admission to 77 per cent when he went home.

On the 11th May, about 9 months after we first saw him, he was admitted for th last time. He had been found semiconscious at home by his doctor who had gone t see him. On admission he was barely conscious and could obey simple commands bu was unable to give any history. There was purpura with ecchymoses in the skin. H had no obvious photophobia but there was marked neck stiffness. The pupils wer small, reacting only sluggishly to light. His haemoglobin was 56 per cent and on thi occasion the white cell count was 8,000/c.mm. with 6,200 polymorphs. A lumba puncture was done and the pressure was 180 mm. of water. Queckenstedt's test wa normal. The cerebro-spinal fluid was turbid, of a greenish-grey colour, and containe 7300 white blood cells/c.mm., more than 90 per cent of which were polymorphs. Th protein was raised, 870 mgm per cent, and the sugar had fallen to 13 mgm per cent. stained film of c.s.f. revealed no organisms and the culture was sterile. He was treate with chloramphenicol and streptomycin but it made very little difference. The tem perature which had been normal on admission rose steadily to 102°F. during the 2 o 3 days before he died. His general condition remained unchanged for about 24 hour but then went downhill. On the 14th May, 72 hours after admission he vomited, think some vomit was aspirated and he died shortly afterwards.

To summarize, this was a man of 60 in whom a tooth socket failed to heal after dent extraction. He was found to have a hypoplastic anaemia, the cause of which was un certain. He showed increased susceptibility to infection and died 11 months after th tooth extraction as a result of an infection, in fact of meningeal involvement. Through out his illness the anaemia and leukopenia had persisted.

Dr. A. B. Raper: For the ten months or so during which this man was unde observation he remained an unexplained haematological problem and in fact he fe into the group which contributes most to unexplained haematological problems, tha of pancytopenia, a reduction of all the formed elements of blood. Dr. Leather ha spoken of the findings when he first came into hospital. At that time he had only 68 polymorphs/c.mm. and his haemoglobin was 53 per cent. But only two days before when he had been sent across from the Dental Hospital by Mr. Snawdon, his poly morphs had been 2700 and haemoglobin was 63 per cent, so it looked at that time a though quite rapid changes had been occurring, and he had been suffering a rapi fall in his red and white cells. When the bone marrow was then examined it was foun that myelocytes were rather more numerous than segmented cells, and that was th finding that Dr. Leather mentioned. We thought this was a change of relatively recen origin and that he was perhaps beginning to recover from a temporary depression granulopoiesis, and that only the future would tell whether this was so or not; but th future revealed that it was not so, for he remained pancytopenic throughout, apar from the influence of transfusion. Marrows were examined at long intervals, the firs in August, the next in November and the third in March. That in November showe a similar picture to the first, but the myelocytes were rather more numerous, the seg mented polymorphs were still scanty, and there were more promyelocytes. There wa obviously a left shift occurring in the marrow to rather more primitive forms, an there were some unidentified cells on that occasion. In March the whole picture ha shifted a little more to the left. There was now a sizable number (8 per cent) promyelocytes, the myelocytes were very numerous (25 per cent), and were accom panied by 8.5 per cent of other cells which somewhat resembled them and which gav rise to some difficulty in classification. It was these cells that made us think of th possibility of plasmacytosis, for in some ways they resembled plasma cells. As you hav heard that possibility was negatived by the finding that there was no Bence-Jone proteinuria, X-ray of the bones showed nothing, and the serum protein pattern wa normal. I eventually concluded that these abnormal cells were micromyelocytes, an this label does raise the question of whether they were actually abnormal leukaemi cells, because one does sometimes see abnormal small myelocytes in the blood and als in the marrow in myeloid leukaemia. In summary, a maturation defect had bee

observed throughout, a piling up of the myelocytes with failure to develop any further, and this became more noticeable as the months passed. Nevertheless at the end of these 3 marrow examinations I wrote: "there is no direct evidence of leukaemia". Whether there was evidence of a change in the direction of leukaemia, and what the bearing of these three marrow investigations on this evidence is, I don't know. I think we had better delay a firm decision until Dr. Tovey has given his views.

Dr. G. Tovey: A sample of this patient's blood was sent to the Regional Transfusion Centre because of the difficulty of deciding whether his blood group was A or O. Now briefly, if you want to decide whether someone is group A you add the patient's red cells to an anti-A grouping serum. If the cells are clumped the patient is group A: if they are not agglutinated the patient is group O. This man's red cells were clumped in such a test so that it looked as if his group was A, but at the same time a large number of the red cells present were just not clumped at all. Those might well be group O cells; hence the difficulty in deciding whether his group was O or A.

Now what might be the cause of this unusual phenomenon? Clearly one might be dealing with a group A patient recently transfused with group O blood. Fortunately, however, the specimen coming from this patient was taken before he was transfused. One might therefore be dealing with a blood group chimera. I am sure you know the chimera, a mythical animal with the body of a goat, the tail of a serpent and the head of a lion. A blood group chimera is a twin who has received some of his fellow twin's blood-forming tissue whilst *in utero*. Two types of haemopoetic tissue are therefore present in his body. One may be forming group A cells and the other group O cells, and so this man might have been a chimera. We were able to exclude this, not only because he denied being a twin, but also by testing whether we could separate the A cells from the O cells. In the case of a chimera, if you add the cells to anti-A all the group A cells will be precipitated and the group O cells left suspended. In the case of this patient however we could not separate the apparent mixture in that way. Thirdly, his blood group might be one of the unusually weak sub-groups of A, the so-called weak A's, (A_3, A_4, A_5, etc.). Blood group substances are not confined to the red cells but are present also in the saliva. An individual who has a weak A in his red cells will similarly have only a small amount of group A substance in his saliva. The patient's saliva was found to contain as much group A as any normal group A individual. The last possibility remained therefore that one was dealing with a patient whose blood group had been changed as a result of disease. This type of change has been seen only in acute leukaemia and in our report to Professor Perry therefore we queried whether this patient might be suffering from an aleukaemic leukaemia.

Dr. W. A. Gillespie: This cerebro-spinal fluid was seen by the resident pathologist during the night, and I saw it the following morning. It was a good sample, with plenty of fluid, and was obviously turbid with numerous polymorphs, as you have heard. The glucose content was quite low, 13 mgm per cent, and this rather suggested that the condition was a diffuse meningitis and not simply a sudden rupture of a brain abscess, which can also give a purulent fluid. However, it proved impossible to find any organisms in the stained smears of the deposit although we examined several slides. We knew that the patient probably had a lowered resistance to infection, as a result of his blood disease; and so we thought that the meningitis might have been caused by an unusual organism which normally would be unlikely to cause meningitis. We had in mind, for example, *Listeria*, which may look like a diphtheroid, and sometimes causes infection in cases like this. We also thought of fusiform bacilli and other members of the *Bacteroides* group, in addition to the organisms which more usually cause meningitis. We therefore put up several cultures anaerobically as well as aerobically and incubated them for several days at 37°C. But all the cultures were sterile. At first we thought that the absence of demonstrable organisms might be due to recent antibiotic treatment, before the patient entered hospital; but this was not the explanation. He had not received any drugs before admission. At the time I did not think that the

failure to find an organism mattered very much because the patient was treated energetically with a mixture of antibiotics which should have been active against any bacteria.

Dr. O. C. Lloyd: This man was wasted. In the serous cavities there was no excess of fluid but there were some old fibrous adhesions at the upper part of the right lung, and in the right lung I found an old healed primary tuberculous complex, with signs of healed tuberculous pleurisy. The heart showed well marked fatty change of the inner third of the myocardium which may have been due to his anaemia. The arteries and veins were all right, but I did note that the post-mortem clot in the veins had separated out and had a very small red component and a large white component; that is evidence of anaemia. The spleen was not enlarged, it was slightly soft and the pattern was normal. He did not have one of those acute splenic tumours you sometimes get with inflammation. The lymph nodes were normal with the exception of one high up in the left cervical chain, which was enlarged. That may well have been the one which Mr. Snawdon mentioned and it was probably reactive hyperplasia from the inflammation which had been going on in his maxilla. The liver, gall bladder, and pancreas were all right. The whole of the gastro-intestinal tract was natural and so also were the urinary system, the genital system and his endocrines. So now let me show you what was wrong with him.

A close-up photograph of the tooth socket in left maxilla (Plate I) shows a certain amount of necrotic bone in the middle of the ulcer. At post mortem I dissected out the anterior part of the left hand side of the face and cut a slice through it in the coronal plane of the body so that it went through the ulcer. The maxillary air sinus has a great thick oedematous lining to it. There is a little bit of swelling and discoloration of the medial side of the orbit where the osteomyelitis which was affecting all of these bones to a greater or lesser extent was rather more acute than elsewhere. It was bursting through into the orbit and into the frontal sinus on that side. All the same I have no doubt that the frontal sinus had been inflamed for as long as the maxillary antrum.

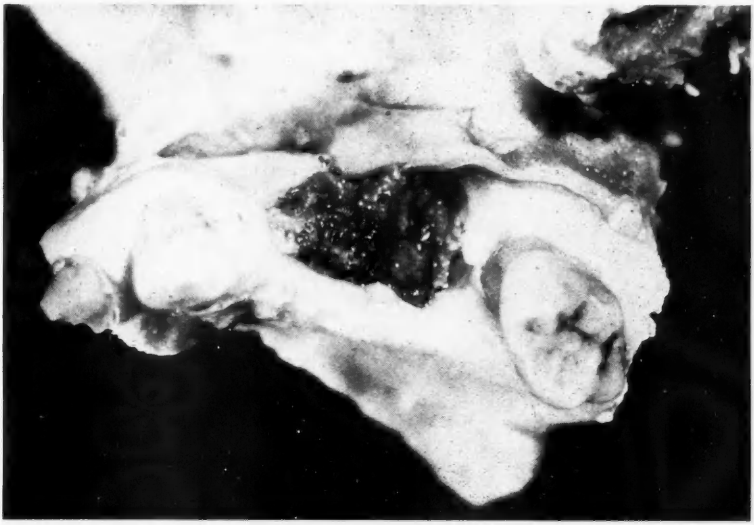
The posterior part of the left frontal sinus was seen to be filled with sticky yellowish necrotic debris. The other frontal sinus was similarly affected and the inflammation spread, through its posterior wall, forming a collection of similar yellowish necrotic material in the mid-line on both sides, just outside the dura mater. On the right hand side this inflammatory process had extended back through into the cranial cavity. The infection had travelled along one of the little emissary veins which goes between the meningeal vessels at that point and the cerebral veins.

A section shows that the cortex of the maxilla is eroded at the point at which the tooth has been pulled out and there is a lot of new bone formation. In the necrotic surface of the tooth socket I found an organism with the morphological appearance of a ray fungus or actinomyces. It is quite likely a pathogenic species of *Actinomyces.*

Plate II shows in the tooth socket a piece of dead bone which would have been sequestrum, if he had been able to get rid of his dead tissue, but he was not able to do so. He had very good healing powers. The squamous epithelium has been growing back all round the fragments of dead bone; the submucosa contains lymphocytes and small round cells, but hardly any polymorphs. "You must get rid of the dirty water before putting in the clean". If you have an inflammation you must get rid of the necrotic material before any healing process can be adequate, and in order to get rid of necrotic material you have to have both active reticulo-endothelial and haemopoietic systems; and *that* was what this man lacked. You must have polymorphs, phagocytes and all other elements working properly or you cannot get rid of necrotic tissue of this sort and the healing process will not be effective. There has been some attempt to remove the bone, since there is a little bit of lacunar resorption, but it has not been very effective.

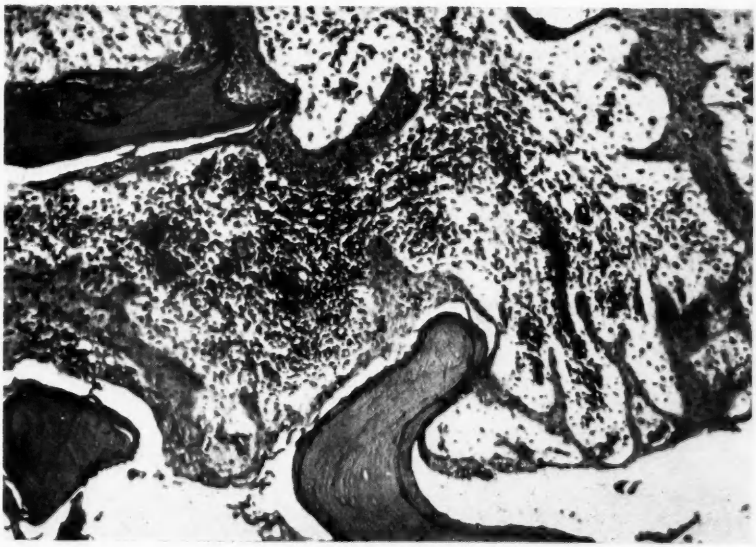
Deep within the maxilla there is chronic osteomyelitis, while in the wall of the maxillary antrum there is a thick layer of oedematous submucosa which contains a

PLATE I



Tooth socket in left maxilla.

PLATE II

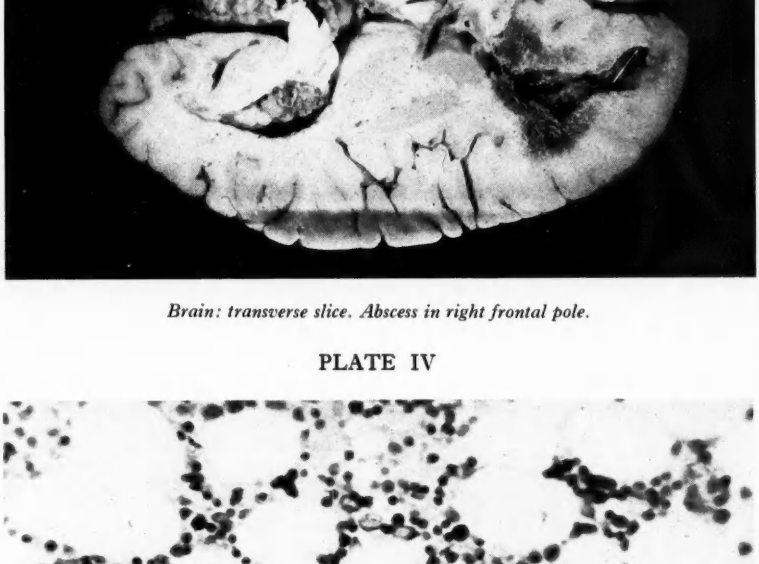


× 100. *Surface of tooth socket.*

PLATE III

Brain: transverse slice. Abscess in right frontal pole.

PLATE IV



× 850. *Femoral marrow.*

fair number of macrophages and other small round cells and just an occasional polymorph here and there. There has been a lot of new bone formation in the lining of the antrum.

In the wall of the left orbit the osteomyelitis is rather more acute, and the connective tissue is very much more vascular. It is granulation tissue and contains lymphocytes and very many more polymorphs than elsewhere. Although this man did not have enough polymorphs to go round he did have some, and they tended to congregate in those places where they were most needed although there were probably not enough of them. Where the inflammation is more acute he was able to do something about destroying his deficient tissues. There is a considerable amount of lacunar resorption going on round these bone fragments.

The frontal sinus epithelium has undergone squamous metaplasia which is a reaction to chronic inflammation. There is considerable formation of new bone under the submucosa. The inflammation crept along one of the communicating veins and entered the brain. Looking at the brain from the outside there was flattening of the convolutions and when it was turned upside down, pus could be seen in the interpeduncular region and around the stalk of the pituitary body. That pus was a greenish colour but the green faded after fixation. It was not the kind of green you get in a *pyocyanea* infection, and was probably due to the presence of inflammatory leucocytes in the pus.

Plate III shows a transverse slice through the brain. A glass rod has been inserted through the hole in the right frontal pole. It enters the cavity of the abscess. In the necrotic wall there are large numbers of petechial haemorrhages. The abscess has burst into the ventricular system giving rise to a generalized ventriculitis. The inflammation went right through the fourth ventricle and out through the basal foramina and so into the meninges below. It was from a septic meningitis that he was suffering and that was in fact the cause of his death. The wall of the abscess microscopically showed a frayed free edge with practically no pyogenic membrane. It was just a quiet necrosis. There was a zone of inflammatory cells and a close examination of these cells showed they were more or less half and half polymorphs and macrophages. He was able to produce some reaction but very little.

I looked at a Gram stain of this section and was unable to detect any bacteria but did see something which I considered to be mycelial fragments. I also looked at a Gram stain of the necrotic material in the frontal sinus and there there were distinct mycelial fragments from a fungus but it is quite impossible to tell what kind of fungus it might have been. You cannot tell that unless you can see the fructification and even then you may not be able to be quite certain. It might have been actinomyces or it might have been monilia. The other thing which I saw in the Gram stain from the frontal sinus necrotic materia! were some rather small and miserable-looking gram positive cocci which were growing in short chains. I do not know whether they had much to do with it, at any rate Dr. Gillespie did not manage to grow it from the c.s.f. during life nor from the post mortem pus from the meninges.

Bisection of the femur showed bone marrow undergoing hyperplasia. A man of this age ought to have yellow marrow practically throughout his femur, but here the upper half of it is red so that it does not look like a marrow aplasia at all. Plate IV shows a considerable degree of reactive hyperplasia in the femoral marrow. Most of the primitive cells are represented but not very many mature elements, in particular there are very few mature polymorphs. The primitive cells include haemocytoblasts and large numbers of myelocytes. There are a few plasma cells and eosinophilic myelocytes are fairly conspicuous in some places. There are numerous macrophages containing iron pigment. Evidently he had been destroying blood rather more rapidly than usual.

Professor Hewer: There was only one granule resembling actinomyces in all your section?

Dr. Lloyd: Just one fragment in the tooth. That was the only fructification anywhere.

Professor Hewer: That might very well be where it commenced, if it was actinomycosis.

Dr. Lloyd: It might, yes.

Mr. Snawdon: I would not say there was anything in this case to make one think clinically of actinomycotic infection. Perhaps I might now clarify two points I should have made earlier: I noticed on his dental record he has a red stamp marked "Idiosyncrasy to penicillin" and although it has no date, judging from the writing and the general wear and tear it has suffered I would put it at about the years 1954–1956. And the other final point: I said the 19th January was the last time I saw the patient for clinical examination. That was true but I should have mentioned that Dr. Barritt did telephone me just after he had come under his care, a few weeks after the last time I saw him that was, to ask one or two points and my views about the case, which were unchanged at that time of course.

Professor Hewer: I take it then that one of the chief clinical points against actinomycosis was absence of numerous sinuses externally.

Mr. Snawdon: There was just nothing. I do not think I have ever seen actinomycosis affecting the mucous membrane. It involves the skin externally when it appears associated with the jaws and face in my experience, and without a demonstrable bony lesion.

Dr. Gillespie: I do not think that this was at all like actinomycosis. We occasionally see cases of actinomycosis, mostly from the Dental Hospital, and in the material one finds colonies of the organisms, the so-called "sulphur granules". There were no such granules seen anywhere in the sections from this case, apart from the one in the tooth socket.

The failure to isolate a bacterium at post-mortem was of course not surprising because the patient had been energetically treated with antibiotics. It was, however, surprising not to find an organism during life before the antibiotic treatment started. I take it that the condition on admission to hospital was a recent rupture of an abscess which had slowly formed in response to invasion by organisms of very little pathogenicity which had died out to a large extent.

Dr. Lloyd: Would that apply to a fungus infection of the brain?

Dr. Gillespie: I don't know. I have never seen a fungus infection of the brain. But do you mean an actinomycotic infection?

Dr. Lloyd: Or a monilial, yes.

Dr. Gillespie: I do not think this was a monilial infection. A monilial infection should have been detectable in the post-mortem material. And the organism would have been easy to isolate. Another point is that fungi and monilia (but not actinomyces) are insensitive to the antibiotics used in this case, and should not have been inhibited by them.

Dr. Leather: Would an actinomycosis, even if it did break out from an abscess, result in an acute picture like this, or would it not be more chronic?

Dr. Gillespie: I think that any abscess, irrespective of its cause, would produce an acute picture if it ruptures and spreads over the meninges.

Dr. Leather: I was just wondering whether an acute process would result in the case of actinomycosis.

Dr. Gillespie: The rupture of an actinomycotic abscess would produce an acute picture, I think.

Dr. Tovey: Five cases have been described showing this type of blood group change and in each case the patient has died of acute leukaemia. One of those patients presented as a pancytopenia, thus closely resembling this patient, but eventually died of acute leukaemia.

The May number of the American Journal of Medicine (1960) contained an interesting article by Carl Moore on the subject of pre-leukaemia, and includes an account of a patient who suffered a refractory anaemia for nearly ten years during which he

received 50 blood transfusions, and then terminally his haematological state changed suddenly to that of an acute leukaemia. Moore stresses that in pre-leukaemia lesions of the mucous membranes fail to heal satisfactorily. The haematological picture may be that of aplasia of the marrow, or there may be a relatively hyperactive marrow similar to that seen in this case at post mortem. The spleen is not enlarged, neither is there any enlargement of the lymph nodes or liver until the terminal acute leukaemia. I would like therefore to suggest that this man was suffering from a pre-leukaemia and that, had he been able to hold on to his tooth, he might have lived sufficiently long to have presented as a case of acute leukaemia.

I think it is a very important case in that, if it is a fact that his was a pre-leukaemic condition, it is instructive to see that the blood group change may be present long before the typical bone marrow changes of acute leukaemia. If a cure is one day found for acute leukaemia, clearly the earlier one can diagnose such cases the better.

Dr. Shaw: May I ask Dr. Raper whether in view of the post mortem findings of hyperactive marrow, he would put this man in that interesting group of refractory anaemias with a hyperplastic marrow? Secondly, could I ask for clarification from Dr. Tovey about why you cannot separate the group A cells from the group O cells?

Dr. Raper: It is true that as he went on his red cell series became more active in his marrow, and in that respect his marrow became hyperactive. But I do not think that was the fundamental change in this case.

Since there has been so much discussion about "pre-leukaemia" I think it might be a good thing to clarify this. What do we mean by pre-leukaemia? We may mean several different things. We can mean a state which inevitably leads on to leukaemia. Now no one has ever detected such a state, and we cannot say with certainty that a given person who has now not got leukaemia will later develop it. Secondly, we can mean (at the other end of the scale) a whole group of conditions which may in some people, and with a small degree of probability, terminate in leukaemia; polycythaemia for instance, and some cases of pernicious anaemia fall into that group. Thirdly we may apply the term to those people who, with a rather greater degree of probability, will become leukaemic. This last is the group into which this patient falls, with a maturation arrest in his marrow and a pancytopenia, for we do know that if we cannot explain this state on other grounds then there is a fair probability that it will eventually prove to be leukaemia. Now what is so interesting in Dr. Tovey's presentation is that he may be succeeding in separating some members of this group and actually putting them into the group No. 1, with an almost complete certainty of development of leukaemia, and so we may find that the application of this test may open up group No. 1, and as he says open up also the possibility of early treatment.

Dr. Tovey: (in reply to Dr. Shaw), The cells which we have been describing as group O are, in fact, not group O cells. They are group A cells modified by disease. As you know, normal group A cells are clumped together by an anti-A serum. These modified group A cells are not clumped by anti-A, but they do absorb anti-A and, as a result, cannot be separated artificially in the test tube.

Professor Hewer: And it is in a case like this where the cells, presumably modified A, are left over, that you are able to show the presence of the A antibody on the surface?

Dr. Tovey: Yes, the A antigen was there and the anti-A could be eluted from the red cells after attempting to agglutinate them with an anti-A grouping serum.

Professor Hewer: And did you in fact elute off the anti-A?

Dr. Tovey: Yes.

Dr. Leather: If this very curious change appears with any frequency in aplastic or hypoplastic anaemias would we not in fact know about it, as most of them are grouped for the purpose of transfusion?

Dr. Tovey: We are investigating this problem with Dr. Raper's help. It is interesting that after we published a similar case from Bristol two years ago when such a change

was considered a rarity, I received several letters from continental blood group workers, and from the States, saying that they are quite certain they have had cases like this in the past but had decided that the patient had a weak sub-type of group A. There is no doubt that these cases have been missed in the past, but again if you have a significant proportion of normal A cells in the mixture and you are not looking very carefully you will mis-group that person as a normal group A.

Dr. Raper: Do you think that such changes are inherently more probable if the patient possesses the A antigen? Of course they are more readily detected in such a case, but are there any means of detecting a change if the patient's blood group is originally O?

Dr. Tovey: No. I can think of no means at the moment if the patient starts group O. One of the odd features is that in all cases the patient has been group A.

Just as a foot note, we are investigating a patient in North Devon, with chronic leukaemia, whom we think has an essentially similar change to this, but in two of her Rh antigens, D and E. Should this prove to be so, this patient is unique as such a change has not been seen before in the Rh groups. It is interesting that the underlying condition is chronic leukaemia and not acute.

Professor Hewer: I have an idea I read recently that leukaemia was commoner among group A than group O. Is that true?

Dr. Tovey: Not really established. Another series has been published which did not substantiate that claim.

Dr. McConnell: Dr. Tovey, did you determine this patient's Rh group?

Dr. Tovey: Oh yes, all the other blood group factors were thoroughly investigated and there was no change in any other blood group antigen.

Notes and News

PROGRAMMES FOR 1961

B.M.A. (Barnstaple Division)

Hon. Secretary: Dr. D. T. C. Barlow, 110 Boutport Street, Barnstaple

25th Jan.: **A symposium.**
22nd Feb.: **A lecture on Steroid therapy and its hazards.**
29th Mar.: **Clinical Meeting:**
26th Apr.: To be arranged.
10th May: **Annual General Meeting.**

B.M.A. (Bristol Division)

Hon. Secretaries: Dr. A. S. Anderson, 10 Leigh Road, Bristol 8 and Dr. H. Temple Phillips, Berkeley House, Charlton Road, Westbury-on-Trym, Bristol

19th Apr.: 8.30 p.m. at Royal Fort. **"Accidents, the uncontrolled epidemic of this century".** By Mr. W. Gissane, CH.M., F.R.C.S.
2nd May: 8 p.m. at Ashton Country Club. Informal Reception.
24th May: (provisional date): **Clinical Meeting at Bristol General Hospital.**
16th June: (provisional date): 4.30 p.m. in the Garden Hall, Royal Fort. Reception for students sitting for final M.B., Ch.B. examinations.
Other meetings to be arranged.

CORNWALL CLINICAL SOCIETY

Hon. Secretaries: Dr. B. A. Gwynne Jenkins, Central Chest Clinic, Tuckingmill, Cornwall, and Dr. H. S. Bennett, Royal Cornwall Infirmary, Truro.

13th Jan.: **Clinical Evening.** Falmouth Hospital.
2nd Feb.: **Clinical Evening.** Royal Cornwall Infirmary.
2nd Mar.: **"The Right to Die".** By Dr. A. E. Clark-Kennedy, M.D., F.R.C.P., Royal Cornwall Infirmary.
24th Mar.: B.M.A. annual lecture. **"Hypertension".** By Professor M. Rosenheim, M.D., F.R.C.P. Royal Cornwall Infirmary.
5th May: **Clinical Demonstrations.** Redruth Hospital.
1st June: Presidential Lecture and Annual General Meeting. Royal Cornwall Infirmary.

DEVON AND EXETER MEDICO-CHIRURGICAL SOCIETY

Hon. Secretary: Dr. F. S. W. Brimblecombe, 6 Barnfield Crescent, Exeter

12th Jan.: at 8.15 p.m. **"Tumours of the Bladder".** Presidential address.
26th Jan.: at 3 p.m. **Clinical Meeting.** Cases available at 3 p.m., followed by tea at 4 p.m. At 4.15 p.m. **"Haematological Diagnosis".** By Dr. J. O. P. Edgecumbe.
Followed by discussion of the cases.
16th Feb.: at 8.15 p.m. **"Some momentous operations".** By Mr. A. Dickson-Wright, M.S., F.R.C.S.
16th Mar.: at 8.15 p.m. **Annual General Meeting and Clinico-pathological demonstrations.**
27th Apr.: at 8.15 p.m. **Clinical Meeting** at the Princess Elizabeth Orthopaedic Hospital.

SOUTH SOMERSET MEDICAL CLUB

Hon. Secretary: Dr. D. M. Barry, X-ray Department, Yeovil General Hospital

19th Jan.: **Dinner and Dance.**
16th Feb.: **"Dermatology".** By Dr. Robert Warin.
16th Mar.: Symposium, **"Deafness".** By Mr. Graeme Allan, F.R.C.S. and Mr. Peter Hugill, F.R.C.S.
20th Apr.: **"Russian Experiences".** By Dr. John Hunt. Joint meeting with College of General Practitioners.

TORQUAY AND DISTRICT MEDICAL SOCIETY

Hon. Secretaries: Dr. D. K. MacTaggart, Health Department, St. Marychurch Town Hall, Torquay, and Dr. J. B. Taylor, Corner Place, Dartmouth Road, Paignton.

28th Jan.: **"How Deaf Children learn to hear".** By Miss Edith Whetnall, M.S., F.R.C.S.
23rd Feb.: **"Portal Hypertension".** By Mr. A. H. Hunt, M.A., D.M., M.CH., F.R.C.S.
17th Mar.: **"The use of Corticosteroids in Respiratory Disease".** By Dr. J. G. Scadding, M.D., F.R.C.P.
13th Apr.: **Clinical Meeting.**
11th May: **Annual General Meeting** at Victoria Hotel, Torquay.
Meetings are held at the Torbay Hospital at 8.30 p.m. unless otherwise stated.